NOVEMBER 1961

Disease-a-Month

Psychoactive Drugs

JACKSON A. SMITH

YEAR BOOK MEDICAL PUBLISHERS • INC.
CHICAGO

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Disease-a-Month

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PRINTED IN U.S.A.

Psychoactive Drugs

JACKSON A. SMITH

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SINCE one of the psychoactive drugs reportedly has been given to 14 million patients in the United States alone, a consideration of these products may logically be preceded by a look at the illness for which they are prescribed. What is this affliction for which 14 million Americans have been treated with one product? It might be presumed that with so prevalent a malady a few million more untreated may still be among us unrecognized. It may be further concluded that in a free and competitive economy other millions must have received similar products under different names since there are presently at least 30 compounds on the market which either retard or accelerate the activity of the psyche.

Any illness which afflicts more than 14 million patients over a period of 6 or 7 years must be regarded as an epidemic of some sort. But, despite the numbers afflicted, this epidemic caused no great stir either professionally or among the laity. Instead, the emphasis was on the "wonder" drugs prescribed to control it.

This enduring epidemic was one of "lost tranquillity." The reason this disorder was a source of only mild interest was because it had been present for such a very long time. Traditionally there has been much more interest in the efforts at treatment than in the illness itself.

TRANQUILLITY.—As the name suggests, the tranquilizers promote tranquillity which is a state of calm, serene composure free from disturbance and accompanied by wakefulness. It is a state certainly to be desired in self but not so appealing in one's employees. Culturally, we hope tranquillity, rather than confusion, will be our lot as we become aged. This same tranquillity is not regularly admired in younger people. Rather, they are taught to be anxious, competitive and concerned. The only people who stress tranquillity as a virtue in children are the neighbors.

This is more an anxious than a tranquil age. The tranquillity of the first 50 years of life may be continually interrupted by concern over the last 15. We seek sufficient security to anticipate any unforeseen misfortune from sickness to our own demise from early life to death. Such concern for the future provides a sustained market for at least a transitory tranquillity. The endless attempt to control the unforeseeable future is one factor that destroys the tranquillity of the present.

Since the awesome moment when man realized that the satisfactions of the day were so temporary that he would have to repeat the entire procedure the following morning, he has been attempting to regain the reassurance this foresight destroyed.

Man had tranquilizers several centuries before he realized the phenothiazines had derivatives. He found that alcohol made him unconcerned, calm and serene to the point of stupor. Aldous Huxley has stated that ". . . primitive man experimented with every root, twig, leaf, flower and fungus in his environment" and that pharmacology preceded agriculture. By the late Stone Age primitive man was poisoning himself in a somewhat systematic fashion and there were addicts before there were farmers.

The quality which produces an uncomfortable nontranquil state is anxiety, which has been defined rather adequately as that "harmful mental state concerned with harm to come."

In the days before there were tranquilizers, other drugs were similarly prescribed for the anxious. By 1850 the effects of bromide on the central nervous system were described and by 1870 chloral hydrate was used in the practice of medicine.

In 1903, an era began which was not unlike the present enthusiastic espousal of the phenothiazines. This earlier enthusiasm

originated with the production of the barbiturates. Eventually 2,500 of these compounds were synthesized and over 50 were marketed!

STIMULANTS.—In addition to those plagued with a lack of tranquillity, the members of another group of patients are judged "too tranquil" and thought to be in need of stimulation. In the recent past, the term "psychic energizers" was applied to a group of compounds which allows serotonin to accumulate by interfering with the enzyme that destroys it. Even more recently, products have become available which similarly energize even though they do not interfere with this enzyme. Obviously, the mode of action of these preparations is not yet totally clear.

These two classes of drugs, those which tranquilize and those which stimulate, will be described separately.

THE TRANQUILIZERS

The tranquilizers act to relieve tension and are indicated for anxious patients. Unfortunately, anxiety is not always easily recognized, and the following remarks are offered in an effort to clarify the clinical picture.

Anxiety has been defined as fear without an object. It may also be evident as an excessive or unnatural fear of sickness, injury or misfortune. The patient is in a state of morbid apprehension which usually is accompanied by autonomic dysfunction.

The patient rarely says he is anxious, but he may complain of fatigue, insomnia or loss of appetite. He may ask for an examination hoping it will dispel the fear that is worrying him. Some say they are "on edge" or "nervous" and don't know why.

Possibly the most frequent symptom of anxiety is an excessive concern over some particular illness. In the male, it may be heart disease, and in the female cancer. These fears may be too disturbing for the patient to discuss. Instead, he may simply say he wants a "checkup." For this reason, it is important for the physician to establish why the patient wants a "checkup" at a particular time. What provoked sufficient concern in the patient to cause him to seek an examination?

Some patients who are severely anxious may not be able to accept the fact that their heart is normal or that they do not

have cancer. They may return to have their heart checked again and again, or they may go to another physician and have the entire examination repeated.

Symptoms found in the anxious include: tinnitus (or "ringing ears"); "blurred vision;" dry mouth; "lump in the throat;" shortness of breath (with sighing respiration); cardiac awareness and palpitations; indigestion or abdominal discomfort; urinary frequency; rectal tension and diarrhea; impotence or premature ejaculation; paresthesias of the extremities ("numbness and coldness of the hands").

Possibly the most disturbing symptom in the anxious is the morbid awareness of self. These patients experience sensations which are unconscious in those who are not anxious and include an awareness of the heart beat and respiration and a preoccupation with their own behavior, memory and ideas. There is an understandable loss of self-confidence.

These symptoms are so widespread that, depending on the interest of the examiner and the concern of the patient, any area or function may be emphasized as primary. The "blurred vision" and "ringing ears" often lead to the patient's first being seen by an ophthalmologist or an otolaryngologist. The abdominal discomfort, nausea and diarrhea or cardiac awareness may guide the patient to the internist. The urinary frequency, impotence or premature ejaculation would be considered significant by the urologist and psychiatrist, although their ideas of the etiology might differ. It is essential, therefore, for the physician's history to include the whole range of the anxious patient's complaints; otherwise, the etiology may not be suspected and a great deal of time and effort may be spent in working out one symptom at a time.

Diagnosis.—The diagnosis rests on the discomfort and concern shown by the patient which are evident in the history. The patient should be questioned about symptoms in all the areas mentioned. The presence of a tachycardia which decreases as the patient becomes more at ease, and excessively perspiring palms and axillae are signs which suggest the diagnosis.

On the other hand, the physician has a tendency to compare the patient's emotional state, response and behavior to his own; the more similar the comparison, the more normal the patient is

judged to be. It is not unusual for a practicing physician who puts in 10 to 14 hours a day to advise patient after patient to "slow down and take it easy." This is sound advice if given for physical reasons, but if the patient is happy and somatically sound, let him work to his heart's content. He does not need a tranquilizer.

Emotionally, it doesn't matter if the patient skips breakfast and exists on a diet of fat meat and eggs fried in butter. If he is comfortable and happy, he is better unmolested. Tranquilizers are indicated for the patient who is obviously "nervous" and agitated *only* if he is uncomfortable.

But a patient may eat three well-balanced vitamin-enriched meals a day prepared with vegetable oil, exercise moderately and be compatible with his wife, and still be so anxious he can't read a newspaper for fear he will see an article about somebody who died of a coronary occlusion. He needs a tranquilizer.

Subjectively, the patient experiences anxiety as apprehension and morbid concern over self and what may happen in the future. This concern is aggravated by an increased response to all stimulation, by an overactive autonomic nervous system and by the intrusion into awareness of sensations that ordinarily are unconscious.

The nonanxious patient is not uncomfortably aware of his heart beat, his respiration, his abdomen nor of himself. The sensations associated with these functions remain unconscious, but in the anxious patient they occupy his conscious state to a morbid degree. Since he did not willfully create the sensations nor the apprehensions and has no idea of their origin, he may find it difficult to ignore or to "forget them."

It would appear that what a man feels continues to take precedence over what he thinks. A sensation still outweights an idea, and as long as his heart palpitates and "feels like it's going to stop," he will find tranquillity hard to come by. Despite his effort to accept the fact that his heart is normal, he still has trouble understanding "why it keeps jumping around."

It would seem likely that only a small percentage of all those who abruptly lose their tranquillity are seen by psychiatrists. Since, in an acute episode, the patient frequently thinks he is either about to run amuck or expire, he always takes the least

traumatic of the two possibilities and decides he is dying. It behooves one to make certain that a patient is only suffering from a loss of tranquillity, since a dead hysteric requires a great deal of explanation.

TYPES OF CHRONICALLY ANXIOUS PATIENTS.—Patients may become anxious for enduring internal reasons not immediately related to their environment. The habitual manner of responding which an individual evolves to satisfy his basic needs for food, shelter and sex may not be carried out in an economic and satisfying manner. Such a patient may be able to reach a temporary state of calm only when he is successfully preparing for anticipated troubles to come. Others find a relief in anger and open conflict. Those of a third group tolerate conflict very poorly and spend their lives seeking tranquillity at any cost.

This continuing inner turmoil may be manifested as follows: There may be a constant preoccupation with future concerns which requires that the patient be continually at work increasing his material security. Such people operate on the premise that "you're either getting ahead or falling behind." Success, instead of offering reassurance, only increases the hazard of a greater failure. Since the insecurity arises from within, the external props merely provide a more comfortable means for being uncomfortable.

In the past, the symptoms of these patients were frequently attributed to overwork (rather than the other way around); and they were advised to "Relax, don't work so hard." Now, they may receive the same advice, but it is made somewhat more feasible by adding a tranquilizer. These individuals frequently are very productive people who seek relief from their inner turmoil by creating an external conflict. Weekends, holidays and too sudden success are poorly tolerated.

Any obvious advice unquestionably is aided by the tranquilizers. For instance, a woman says she understands her problem. For 10 years she has been married to a man she hates. If she has not thought of divorce during this period, she should be suspected of being defective. Therefore, if in a flash of insight divorce is offered as the solution to such a problem, it will certainly be more effective if given with a tranquilizer.

Other less productive individuals vent their irritation by seeking

and finding unending interpersonal conflicts. The only emotion they can comfortably and safely express is in the form of criticism. They are of particular interest when they marry an individual of the opposite temperament, a person who dislikes argument. This type of marriage creates an unusual balance with one individual seeking conflict and the other constantly trying to avoid it. Such couples seldom need a hobby; they have each other. They may need a tranquilizer and it isn't too material which partner is treated.

Some people seemingly spend their lives in fear of the retaliation or retribution that might result from an expression of the hostility they feel. Their tranquillity is entirely external, and concealing the inner resentment may be chronically fatiguing. This accepting attitude makes them vulnerable to whatever impositions a more aggressive parent, wife or employer may inflict. These people take pride in their outer calm. For instance the lady who says that in 30 years of marriage there has never been a cross word between her and the spouse, implies a most unusual relationship in which one partner must be extremely tolerant, a deaf mute devoid of affect or a husband who resides in the other half of the duplex.

In other instances, the dependable, ever-available daughter in the large family, who never marries because "someone has to look after the folks," finds her efforts are expected rather than appreciated. This does not promote tranquillity. Then there is the secretary who gives up her day off to get the work done, or the aunt the relatives call when someone in the family is sick. Such people by their passive attitudes are extremely vulnerable to imposition.

EXTERNALLY LOST TRANQUILLITY.—In addition, tranquillity may be lost because of disturbances or conflicts arising in the external environment, such as a severe illness in, or death of, another person similarly situated, or a failure to express anger for conscious reasons.

To illustrate these possibilities: The longer an individual lives, the fewer of his contemporaries survive and the more meaningful illness and death become. In the young, the death of a peer is unusual and a tragedy; in the aged, the same event is a commonplace. Besides the expected depression which attends the death

of a friend, the survivor is also made anxious by the fear he may suffer a similar fate.

For these reasons, an anxious patient should always be asked if a friend or acquaintance has been ill or has died, because the patient may seek a "checkup" to reassure himself he is not developing a similar condition. If the patient says that an acquaintance or a neighbor has recently died following a coronary occlusion, this is sufficient. The examining physician should not belabor the point or offer any detailed reassurance to the patient. All that is necessary is for the patient to recount it. He presumes his physician will make sure he is not similarly afflicted.

Finally, an adult can express his anger only with due regard for his mundane but prevailing need for food, shelter and security. Although not often mentioned, situations do arise which destroy tranquillity and do not lend themselves to easy solution. Such situations account for a sizable group of tranquilizer takers.

For instance, a new supervisor starts out to set a production record by berating those under him. Many of those berated may be angry, but seniority, a family, debts and age may cause them to forego the pleasure of expressing their hostility. In other instances, a mother-in-law drops in for a month for a condescending visit with a daughter-in-law. By the end of the visit, the entire household is irregular, and the only time the daughter-in-law is tranquil is in her relations with her husband.

THE CHRONIC OFFICE PATIENT.—Patients whose chronic complaints have weathered many a therapeutic attack may be tried on tranquilizers, as they were on vitamins, and before that on bromides and barbiturates. Diagnosis is not a great problem in such cases. The history is clarifying, because they have been treated by a series of physicians for an extended period for one complaint or another. In the past they were called hypochondriacs.

These patients show a superficial familiarity with medical terms and drug names. They resent any implication that their own diagnosis for which they request treatment is incorrect or in need of confirmation. They may be angered by the fact that the physician fails to show the same surprise, interest or wonder over their complaints that neighbors, relatives or members of the lay public do.

Such patients are not a source of great satisfaction in treatment. Frequently they get neither better nor worse, but maintain an exasperating and demanding state in which one complaint is dropped only as it is replaced by another. This situation is particularly stimulating to the physician if the hypochondriac utilizes the waiting room, with other patients as an audience, to describe in minute detail the lack of improvement she has experienced. This situation will usually lead to rapid tranquilization.

Patients who are plagued with fears, who are chronically dissatisfied with themselves and who gain little pleasure from living may conclude that all their inadequacy, displeasure and apprehensions arise from the fact that they are ill. The fact that the physician fails to find proof of their illness presents no great problem, because he either failed to make the right "test" or he was not expert enough to locate the trouble. He must be wrong because they do not "feel" any better. The patient considers himself to be physically sick. He has the subjective sensations to substantiate his conclusions, and he is seldom pleased with those who fail to agree.

Mode of actions.—In general, drugs may either stimulate or depress physiologic or biochemical functions to alter the course of an illness in a predictable manner. They may inhibit enzymes or they may accelerate or retard cellular activity, but they do not provide new functions. Ideally, all these factors about a drug as well as its absorption, intermediary products and excretion would be known. Unfortunately, this ideal state of knowledge is seldom attained.

Unlike the sedatives which were available earlier, the phenothiazine derivatives and the rauwolfia alkaloids do not produce ataxia, anesthesia, excitement or any pronounced tendency to addiction. They also differ in that they increase muscle tone and lower the seizure threshold. The glycerol derivatives are effective skeletal muscle relaxants.

It is generally agreed that these are nonspecific remedies. Tranquilizers control symptoms rather than alter etiology.

Clarifying the effectiveness of the tranquilizers is made difficult by the lack of objective measures which may be applied to emotionally ill patients. Only in extreme, chronic cases is the natural course of these illnesses so predictable as to attribute minor

symptomatic changes to a particular treatment. In some emotionally ill outpatients, the symptoms assume a major function in the patient's pattern of living until one may justifiably ask, "How would this patient be able to continue without any complaints?" The picture is further clouded by the tendency of many of these disorders to be self-limiting or episodic. The influence of suggestion varies from one patient to another, with the personality of the physician giving the drug and with his faith in the effectiveness of the medication.

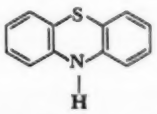
As in other disorders in which the etiology is not clear and in which a prolonged interval may elapse between the injury and the appearance of the symptoms, the effectiveness of a particular drug may be very hard to establish.

Types of Tranquilizers

Possibly the simplest method of grouping the numerous tranquilizing compounds would be under three headings: (1) phenothiazine derivatives, (2) rauwolfia alkaloids and (3) others, which include the glycerol derivatives, the diphenylmethane derivatives and those compounds which do not fit into other groups.

To be totally conversant with the formulas of all the available drugs in these groups would require that the clinician be an interested biochemist. Therefore, only the phenothiazine nucleus and the differences between a few of the derivatives are given. A similar pattern is followed with the rauwolfia alkaloids.

Phenothiazine derivatives.—Figure 1 shows the phenothiazine nucleus. To this nucleus either an aliphatic, a piperdine or

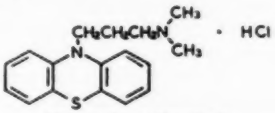


Phenothiazine Nucleus

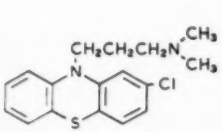
Fig. 1

a piperazine group may be added. The additions to this nucleus are made at the 2- and 10- positions indicated. Unfortunately, the results of these additions are much more apparent chemically

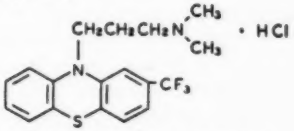
than they are in the patient's response. Figure 2 shows the structural formulas of 3 phenothiazines.



Promazine (Sparine)



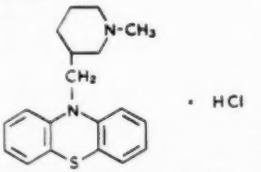
Chlorpromazine (Thorazine)



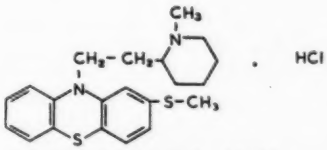
Trifluopromazine (Vesprin)

FIG. 2

Figure 3 shows other compounds are formed by adding a piperidine "tail" to the phenothiazine nucleus. Thioridazine hydrochloride (Mellaril) and mepazine acetate (Pacatal) are such compounds.



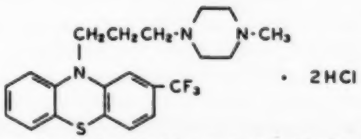
Mepazine hydrochloride (Pacatal)



Thioridazine hydrochloride (Mellaril)

FIG. 3

Figure 4 shows phenothiazine derivatives which have a piperazine "tail." Trifluoperazine hydrochloride (Stelazine) is such a compound.



Trifluoperazine hydrochloride (Stelazine dihydrochloride)

FIG. 4

Side effects produced by phenothiazine derivatives.—The side effects which these compounds produce are numerous, widespread and vary with the patient and the dosage. Most frequently they produce lethargy or excessive sedation. They may also cause tachycardia, hypothermia, dryness of the mouth, hypotension, photosensitivity and rarely may even cause the virtuous to lactate. Extrapyramidal symptoms include weakness, loss of associated movements, excessive salivation and painful muscle spasm. These findings become more marked with larger doses.

The side effects may be controlled by decreasing the dosage or by giving an antiparkinsonian drug to relieve the extrapyramidal symptoms. Parkinsonism, jaundice and photosensitivity reportedly are not a problem with thioridazine hydrochloride (Mellaril).

Choice of a phenothiazine derivative.—The most desirable product is the most active drug with the fewest undesirable side effects. It is not feasible for the physician to be equally familiar with all the available compounds, and ordinarily he will narrow his choice to one or two drugs with which he becomes familiar and in which he has the most confidence.

If the first tranquilizer given is a potent compound and the patient fails to respond, *there is no need to give a series of similar drugs with different names.* Usually if the patient does not respond to one phenothiazine he will not respond to another.

Although there are exceptions to this statement, other factors besides the drug may enter the picture. For instance, a patient may be given a tranquilizer and fail to improve, but 2 or 3 months later another physician may try a different compound and the patient may report a marked change for the better. In the meantime, the patient's illness may have altered, the home situation may be different or the second physician may be more persuasive.

Differences in the various phenothiazine derivatives.—From time to time, a new tranquilizer is introduced which is said to have a more marked effect on certain symptoms than products previously available. This degree of specificity of action is questionable. The most significant differences between the phenothiazines are in their potency and in the side effects they produce.

As an example, a comparison of mepazine acetate (Pacatal) and chlorpromazine (Thorazine) shows the following differ-

ences: mepazine acetate does not lower the body temperature in rats, nor does it antagonize the "waltzing syndrome" in mice nor even augment the carotid sinus reflex in cats as does chlorpromazine. Pharmacologically, this is undoubtedly significant, but in the practice of medicine it is hardly sufficient reason to give one compound in preference to the other.

Dosage.—The minimal daily oral dose suggested by the manufacturer is sufficient to begin with. If after a week no improvement or side effects are noted, the amount taken each day may be increased to the next suggested higher dosage. This rate of increase may be continued over a 4–6 week period until the maximum recommended dose is reached. If improvement or side effects develop during this interval, the patient should be maintained on the amount being given at the time this change occurred. The patient should be seen weekly during this initial trial, and leukocyte counts may be made at the time of each visit.

Usually the patient will decrease his drug intake as he feels better, but some patients may want or need to take the drug regularly for a prolonged period. These compounds are well tolerated once the dose is established. If necessary, they may be given safely for protracted periods.

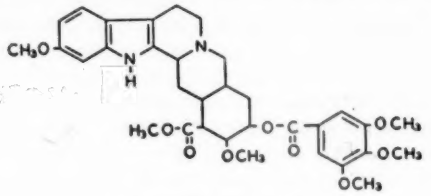
When these compounds are administered parenterally, they should be given by deep intramuscular injection. The more disturbed the patient, the more of the drug he will require. As soon as circumstances permit, the medication should be given orally.

RAUWOLFIA ALKALOIDS.—*Rauwolfia serpentina* is a climbing shrub indigenous to India and adjacent countries. The powdered whole root has been used for centuries for various disorders including mental illness. In 1931, a number of the active alkaloids were isolated.

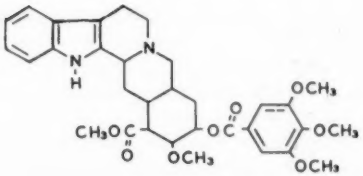
The use of reserpine in the treatment of the mentally ill was advocated in the United States at about the same time as the phenothiazine derivatives were introduced. The actions and the side effects of these compounds are in many ways comparable. But the interest in reserpine preparations has not kept pace with that shown in the phenothiazine derivatives.

These compounds produce a nonhypnotic sedation. They also exert an antihypertensive effect accompanied by bradycardia. The mode of action in the central nervous system presumably

results from a suppression of sympathetic predominance near the level of the hypothalamus. The structural formulas of two rauwolfia alkaloids are shown in Figure 5. Reserpine is available under several different names. In addition, structurally modified compounds as shown in Figure 5 are obtainable also. There are no specific differences in the indications for the use of these products.



Reserpine (Serpasil)



Deserpidine (Harmonyl)

FIG. 5

Side effects of the rauwolfia alkaloids.—These include nasal stuffiness, weight gain, diarrhea, dryness of the mouth, paradoxical anxiety, depression, fatigue and a sense of weakness and increased secretory and motor activity of the gastrointestinal tract. The last complication may be of concern in patients with a history of gastric ulcer. Extrapyramidal symptoms are frequent and sodium retention with edema has been reported.

Choice of drug and dosage.—Since the potency, actions and side effects of these products are quite similar, the physician may use the drug with which he is most familiar. It has been suggested that from 10 to 14 days are required for the optimal dosage to be determined in the anxious when these drugs are used. It would seem wiser to be cautious than heroic in the beginning and

to use the minimal recommended oral dose in outpatients for 2 weeks before increasing the amount to the next recommended level. The oral route is preferable; if parenteral administration is necessary, it should be by deep intramuscular injection.

Other Compounds Used to Tranquilize

Other tranquilizing compounds include glycerol derivatives, diphenylmethane derivatives and some that do not fit comfortably into any of the previously mentioned groups. The mode of action of these compounds is difficult to clarify. Their most frequent effect is to relax skeletal muscle and thereby to reduce tension, but not all possess this property and at least one is a stimulant.

The glycerol derivatives.—These compounds include Equanil and Miltown (meprobamate) which should be equally active by either name. Phenaglycodol (Ultran), isopropyl meprobamate (Soma) and mephenesin (Tolserol) are several of the others in this chemically similar group.

The reports on these compounds vary but they are routinely encouraging, that is, if the studies are uncontrolled. They are advertised for tension and "nervousness," low back pain and generally for any symptom which persists without any demonstrable physical cause. These drugs offer symptomatic relief and do not alter the etiology of the complaints for which they are recommended. Like most other nonspecific remedies, they are advocated for the alcoholic. As they are infrequently habituating, they are superior to many of the earlier products recommended for these patients.

Choice of glycerol derivatives.—The greatest difference in these compounds seems to be in their side effects. Meprobamate (whether Equanil or Miltown) may produce hypersensitivity reactions including urticaria, maculopapular rashes, intense pruritus, and chills and fever. It has been recommended that this drug be given cautiously to patients with a history of allergy. In addition, some patients apparently develop a tolerance for meprobamate after prolonged administration. Withdrawal symptoms including convulsions have been reported and in some a physical as well as a psychic dependence may occur.

Phenaglycodol (Ultran) is similar in action to meprobamate. Both have a common chemical derivation from mephenesin (Tolserol), but phenaglycodol reportedly is less toxic.

In addition to the individual use of these drugs, they are also offered in various combinations with estrogens, aspirin and other compounds. They may be given in a slow-release capsule in which one dose lasts the entire day. Since the effects are difficult to evaluate in the usual dosage form, an attempt to comment on the advantages of the long-acting variety would only compound the confusion.

The most desirable of these skeletal muscle relaxants should be the most potent product with the fewest undesirable side effects. If a patient does not respond to one, there is no reason to subject him to the entire list presently thought to be active. All of these compounds are relatively well tolerated on prolonged administration.

The dosage should be the average recommended daily intake. A trial of 2 weeks is sufficient, and if the patient has not shown evidence of improvement at the end of this period, there is little reason to continue the compound.

As an example of the placebo effects of these drugs, a patient who had been on meprobamate for 6 months was included in a "double blind" study using two of these compounds and an inactive placebo. This patient complained bitterly because he did not receive meprobamate which had "helped" him so much when he was taking it. When the study was completed, it was found that the patient had been receiving meprobamate during the entire interval.

Generally, the phenothiazine derivatives and the rauwolfia alkaloids have been termed the "strong," "major" or "potent" tranquilizers, whereas the others (such as glycerol and diphenylmethane derivatives), including meprobamate and phenaglycodol, have been called the "minor or weak tranquilizers." For some reason, they have not been termed impotent as compared with those more potent.

The actions of the potent tranquilizers are more clear cut and so are their side effects. But this does not imply that the potent group should be given only to the most obviously disturbed. The potent tranquilizers at lower doses have few side effects and may

be much more effective than the weaker compounds at the maximum recommended dose.

A disconcerting revelation about some of the newer compounds was that they are both stimulating and tranquilizing while still others are "normalizing." One might presume that any product which tended to correct an extreme, whether the extreme was of the nature of overactivity or retardation, would be "normalizing."

DIPHENYLMETHANE DERIVATIVES.—Hydroxyzine (Atarax) and benactyzine (Suavitil) are compounds that have some quieting actions or tranquilizing properties. Their side effects, too, are relatively mild. Pipradol (Meratran) has the opposite effect and is a stimulant.

Other diphenylmethane derivatives.—Some of the more interesting, recently developed compounds are in this group. Chlordiazepoxide (Librium) is such a drug. It has a tranquilizing effect with very few side effects and appears to be more potent than some of the skeletal muscle relaxants. The compound has been used extensively in the treatment of various types of anxiety tension states and the early reports are most encouraging. The most frequent side effects are drowsiness and ataxia which are controllable by altering the dosage. Habituation has not been reported and the product has much to recommend it in the treatment of the alcoholic.

One of the most recently introduced compounds for the treatment of anxiety is hydroxyphepamate (Listica). It is described as being safe and long-acting, and is called a noneuphoriant, nonhabituating tranquilizer. There are no stated contraindications. Drowsiness may occur but is infrequent and is controllable by altering the dosage.

SUMMARY ON THE TRANQUILIZERS

Because of such factors as suggestion, spontaneous changes in symptomatology and the problem of measuring improvement, the evaluation of tranquilizing medication in anxious outpatients is most difficult. Consequently, the early reports on some of these compounds have been much more enthusiastic than more controlled studies done at a later time.

The introduction of the tranquilizers ushered in an unprece-

dented era of name-coining. As the list of tranquilizers grew longer, new words that somehow implied relaxation became increasingly more difficult to create. Some of the more euphonious efforts have included Placidyl, Harmonyl, Moderil and Notensil. Undoubtedly, these terms are preferable to such names as "Frenzydyl" or "Tilted" but they are no more meaningful. The present situation is comparable to attempting to think up 20 different and distinctive names for aspirin without ever saying aspirin.

In addition to the problem of finding a trade name, there has been the problem of describing these substances. After the first 10 similarly acting compounds became available, the practitioner showed a certain degree of resistance to hearing about the next dozen tranquilizers. Such semantically sound terms as ataraxics, psychoinhibitors, psycholeptics and neuroleptics have been offered; or a drug may be described as simply more effective than the other tranquilizers without straining for a specific name. Most physicians are much more interested in the actions than the title. For instance, those down-wind to an Artiodactyla Capra would find the male goat smelled no more sweetly in Latin or Greek than in Anglo-Saxon.

STIMULANTS

Before discussing the compounds which stimulate, it seems desirable to consider first what types of patients need to be stimulated. One large group that may be in need of some sort of "lift" includes those chronically fatigued patients who are always weary and never rested. In a second group the patients are less weary but do not enjoy living and therefore are not impelled to activity. Others need stimulating because they are immobilized by complaints which have no demonstrable somatic reason for their existence. Finally, the most chronic and the most lacking in the ability to function are the apathetic, anergic schizophrenics who people the wards of state mental hospitals.

A major problem for the practitioner in deciding which drug to prescribe has been created by the confusion in classification that has grown up with dynamic psychiatry. For example, at one psychiatric meeting on depression in 1958, 13 types of depression were described and 5 more were suggested.

TYPES OF DEPRESSION.—Avoiding the minutiae of discord over

classification, there is general psychiatric agreement that two types of depression exist—reactive and endogenous. In a reactive depression the patient has suffered some personal loss which in the doctor's judgment is sufficient and fitting to cause the patient's sadness. This may be a death in the family, financial reverses or some other loss of security. Kraepelin questioned the concept of reactive depression and cited the case of his patient who was first depressed after her husband's death, was equally saddened after her dog died and was no less so when her pet bird perished.

An endogenous depression arises primarily from within, and the patient is unable to recount any cause for his sadness.

From the time of Hippocrates, sustained and abnormal changes in the moods of men have been observed and recorded. Those so affected were thought to have an excess of "black bile" (i.e., melancholia) and were said to be taken with a "pensive sadness."

For the past century, the tendency of depressive states to be cyclic, self-limiting or recurring has been recognized. Kraepelin emphasized that although these disorders were inclined to recur they did not progress to an emotionally deteriorated state. *In the treatment of any recurring illness, the phase in which treatment is initiated is of great importance. Any treatment given during the recovery phase will be successful if given long enough for the illness to run its course.*

Of late, most of the advertisements of stimulating drugs have limited their recommendations to such unqualified terms as nervousness or fatigue. Other companies have simply relied on excellent quotations from Milton or Shakespeare which the physician may apply apparently to whomever he likes. The latter approach has much to recommend it.

Fatigue, nervousness and depression are terms with which the practitioner is supposed to be intuitively familiar; just how he gains this intuition is somewhat less clear. "We have the convention that we may all use such terms with any shade of meaning which we like to give them from moment to moment. No definitions are required, nor are we supposed to have any historical sense of how they came into use. So we have a form of semantic ataxia, in which we stagger from one vagueness to another. The stepping stones across the stream of ignorance often turn out to be foam heaps of an outmoded form of scientific detergent." This

criticism by Gooddy of "syndromes" is equally applicable to these psychiatric terms.

DIAGNOSIS.—Deciding whether a patient is depressed or anxious depends on which symptoms predominate. The depressed individual may show a psychomotor retardation, that is, he is slow to answer and slow to move. He looks sad. Frequently he is hypochondriacal. A marked element of self-criticism, self-doubt and loss of self-esteem is present in most of the melancholy.

These are not the times for weeping and wailing and gnashing of teeth, and usually the depressed attempt to conceal the depth of their misery. The more stable the patient, the more discomfort he can tolerate without complaint—a fact which unfortunately accounts for many unexpected suicides.

Typically, a depressed patient may have trouble defining his complaints. Usually in response to a question about his symptoms, the patient replies, "I don't know what's wrong with me; I can't get anything done anymore" or "I've slowed down, and I don't enjoy anything the way I used to." Patients who are "slowed down" as compared with their usual energy output and activity, the chronically fatigued and those whose complaints have not responded to other treatment are those usually singled out for treatment with one of the newer stimulants.

EARLIER STIMULANTS OR ENERGIZERS.—Various compounds have been used in the past in the attempt to improve the mood and increase the energy output of depressed patients. These include opium, strychnine, atropine and ergotamine, barbiturates, metrazol and amphetamine. In 1934, it was thought that the administration of hematoporphyrin increased the patient's available energy and was greeted with considerable enthusiasm as a treatment for the depressed. In the late 1940's, intravenous ether was recommended similarly.

ACTIONS OF THE NEWER STIMULANTS AND ENERGIZERS.—The exchange and transfer of energy is rather poorly understood in the physical sciences; it is more difficult to study in physiologic processes. Precisely how the energizers act has become less clear as they have been intensively studied, and some of the "psychic energizers" seem to be taking on an anergic hue.

The interest in "blocking agents" began with observations on the metabolism of serotonin. For instance, it was found that a

known hallucinogenic agent, lysergic acid diethylamide (LSD), was a powerful antagonist of serotonin. From this it was postulated that serotonin was necessary to maintain sanity. Brodie observed that reserpine liberated cerebral serotonin which was associated with its tranquilizing effects. The first stimulant of this group, iproniazid phosphate (Marsilid), also increased serotonin by blocking the enzyme monoamine oxidase which destroyed it. This seems somewhat paradoxical since reserpine tranquilized and iproniazid energized, and both caused serotonin to accumulate. But this was a minor paradox and iproniazid was introduced as the first "psychic energizer." It is worth noting that iproniazid had been used previously in the treatment of tuberculosis and was known to be a very toxic drug.

Page, after reviewing over 500 articles on serotonin, concluded that this substance played some part in the function of the normal brain but that this function was unknown. He added that the evidence in favor of disturbed serotonin metabolism in mental disease was not strong.

Several energizers or stimulants are available which have this property of blocking monoamine oxidase and allowing serotonin to accumulate. In addition, there are several other energizers available which do not interfere with the metabolism of serotonin. Reportedly they are equally effective.

REPORT ON THE EFFECTIVENESS OF THESE PREPARATIONS.—In the treatment of emotional illness two factors must be continually kept in mind—the effects of time in a self-limiting or an episodic illness and the force of other factors on the patient's symptoms besides the particular treatment being tried. This is true with drugs, but it is no less important with psychotherapy.

The reports on the results of treatment with the various newer stimulants are unusual in the variety of answers found by several investigators using the same drug. As an example, two reports in the same journal (Am. J. Psychiat., vol. 116, 1959) on the same drug showed the following: one investigator, King, concluded, "Indeed this study raises the question as to whether phenelzine (Nardil) is of any benefit in depression"; but the second group of investigators, Saunders *et al.*, reported, "Almost without exception, patients with endogenous (essential, true, primary) depression responded favorably to phenelzine (Nardil)."

This degree of variation in the findings is perplexing, to say the least. Another report stated that 46 of 50 depressed patients treated with iproniazid showed a partial or full remission. The author described these results as "astonishing"; with this conclusion there can be no argument. But it may be presumed that the ideal stimulant or energizer has not yet been found or there would not be 10 or 15 similar compounds on the market.

The practitioner may be mildly irritated when he prescribes a drug which according to an advertisement has been proved effective in 500 published reports only to have his patients complain that nothing happens when they take the pills. Part of this confusion results from a lack of control of the studies reported and the failure to carry out a followup to see how lasting the improvement was.

The best example of how important a followup is in the treatment of patients with emotional problems is in the management of the alcoholic. The effectiveness of a particular treatment with this group of patients apparently *depends on how soon after treatment the results are tabulated.* A week after treatment is initiated the results usually are excellent, the patients are enthusiastic and everyone is happy. After 2 months the results are good; but after 6 months they may be only fair, and after 18 months a new approach is recommended.

A followup study with any form of therapy is essential but seldom encouraging. One investigator, after offering an enthusiastic report of a new drug, was asked if he did a followup, and he replied, "I did once, but never again."

Another factor in these reports is the tendency to report the patients who improve, without sufficient emphasis on those who do not change. In many studies, patients may show marked improvement, moderate improvement, mild improvement and questionable improvement, or they may be worse. On such a scale, the odds favor improvement.

Some reports are "testimonial" in type which makes Pierre Janet's observation on testimony worth repeating. He concluded that if all that was required to establish a fact was testimony, the most certain event in history was the existence of the devil; because during the Middle Ages, "he" was seen and described by more people than any other individual.

HYDRAZINE DERIVATIVES.—The hydrazine derivatives include phenelzine (Nardil), nialamide (Niamid), isocarboxazide (Marplan), iproniazid (Marsilid) and *alpha*-methylphenethylhydrazine (Catron). All these compounds have two features in common: they inhibit monoamine oxidase and their use is contraindicated in patients with a history of liver disease. There is considerable doubt as to the importance of their blocking of monoamine oxidase, but there is no question of the need to be alert to the possibility of a toxic hepatitis from these drugs.

The suggestion that the physician should continue therapy with these products for 30 days or more before becoming discouraged if improvement does not occur seems excessive. It would appear that a patient would have to be desperate indeed to continue to take a medication and to endure the misery of a depression for 30 to 60 days waiting for some vaguely anticipated relief.

The history of the use of these compounds in depression is interesting. Apparently, Kline's original enthusiastic report on iproniazid was based on a group of chronic anergic schizophrenics. But iproniazid is not presently recommended for schizophrenics even though they certainly do need energizing as often as they need tranquilizing. Of late, these hydrazine derivatives have been recommended specificially for depression. Just what produced this alteration in therapeutic enthusiasm is not clear.

It may result from what Foulds described as a psychiatric willingness to put the humanitarian cart ahead of the scientific horse. As a consequence of this willingness, those patients most likely to recover spontaneously are soon definable as those for whom a given treatment is most indicated.

Choice of a hydrazine derivative.—If the physician feels the need to prescribe one of these compounds, he should choose the drug with the fewest disturbing side effects. Phenelzine, nialamide and isocarboxazide apparently are the least toxic although Benack and Lynch in 1961 reported a case of jaundice after treatment with isocarboxazide (Marplan) and Knight in 1961 described a similar occurrence.

The toxicity of iproniazid and *alpha*-methylphenethylhydrazine

is known and there is no indication for giving either of these compounds when similar and less hazardous products are available.

These preparations should not be hastily given. If a patient has not responded to other stimulants or to electroshock treatment and is showing no evidence of improving, then phenelzine, nialamide and isocarboxazide may be considered.

Side effects of the hydrazine derivatives.—The development of jaundice in a patient receiving one of these compounds is an ominous sign since it may be followed by a fulminating hepatitis. Liver function tests must be done regularly in patients receiving these compounds. As previously noted, the drugs are contraindicated in patients with a history of liver disease.

Other side effects which may be seen include hyperactivity, inappropriate behavior, toxic states, hypotension which may be severe, dryness of the mouth, blurred vision, impotence and palpitation. Such neurologic side effects as hyperreflexia, clonus, tremors, vertigo and syncope have been reported.

OTHER STIMULANTS.—These include amphetamine, imipramine hydrochloride (Tofranil), methylphenedate hydrochloride (Ritalin hydrochloride), deanol acetamidobenzoate (Deaner), pipradral hydrochloride (Meratran hydrochloride), combinations of meprobamate and benactyzine hydrochloride (Deprol) and amitriptyline hydrochloride (Elavil) which do not inhibit monoamine oxidase. Two other compounds, transcyclopromine (Parnate) and etryptamine acetate (Monase) do inhibit monoamine oxidase, but they are not hydrazine derivatives and should not be as potentially toxic to the patient's liver.

The amphetamines.—These compounds may be of some help in mild depression of short duration. They mask fatigue and produce a sense of well-being, followed by a drop in mood when their effect wanes. Whenever a patient is started on one of the amphetamines, the practitioner should have some definite plan in mind for terminating the drug.

The prolonged administration of these compounds is likely to lead to habituation in susceptible patients, including physicians. Hampton, in 1961, reported that of 31 patients who had taken these compounds for 2 years or more, 10 were physicians, 1 was

a nurse and 2 were physicians' wives. The amphetamines are not the answer for the chronically unhappy, the poorly adjusted, nor the individual who is forever fatigued. The risk of habituation contraindicates their use in the alcoholic. The side effects include habituation, sleeplessness, tachycardia and anorexia.

Imipramine hydrochloride (Tofranil) is reportedly helpful in depressed patients, is seemingly potent and has few disturbing side effects. Imipramine should not be given in combination with monoamine oxidase inhibitors or to patients with increased intraocular pressure. Incidents of tachycardia in patients receiving this drug are apparently controlled by reducing the dosage. Amitriptyline hydrochloride (Elavil) is another product recently offered as a potent antidepressive. The side effects reportedly are mild and include drowsiness, vertigo, nausea, epigastric distress and anorexia.

Both transcyclopromine (Parnate) and etryptamine acetate (Monase) inhibit monoamine oxidase, but since neither is a hydrazine they should not have the potential liver toxicity of these compounds. Such side effects as hypotension, gastrointestinal disturbances, blurred vision and tachycardia have been reported with these drugs.

Possibly the safest of the group is Deprol (one of several combinations of meprobamate with other compounds, in this instance benactyzine). Its side effects are quite mild but so are its effects. In my experience with several cases of severe depression who were hospitalized and under the usual precautions to prevent suicide, the efficacy of Deprol was not confirmed. These patients showed no observable change, prompt or otherwise, with this compound; neither did they show any side effects.

Since these compounds are nonspecific and their mode of action in patients is generally vague, an immediate question would be how long they should be continued and in what type of patient. Theoretically, a patient with a depressive episode who was relieved by one of these stimulants could be continued on the drug until he recovers. Since these compounds (except for the amphetamines) have a low tendency to habituation, they could be safely continued for several weeks or months.

Summary on the Stimulants

The use of stimulating drugs presents several problems which include the types of patients for whom they should be prescribed, determining the effectiveness and safety of the compounds presented, and the hazard of suicide in the patient who does not respond immediately.

No differentiating tests are available for depression and the basis for selection of patients for trial on these compounds rests on clinical judgment. It should be emphasized that those depressed are frequently anxious as well, and that depression may be a feature in somatic illness as well as in other primary emotional disorders.

The monoamine oxidase inhibitors which are hydrazine derivatives are of particular concern because of the possibility of hepatitis. These compounds include phenelzine (Nardal), nialamide (Niamid) and isocarboxazide (Marplan). Two others of known toxicity, *alpha*-methylphenethylhydrazine (Catron) and iproniazid phosphate (Marsilid), should not be used because the other three are less toxic and similar in action.

A severely depressed patient should be hospitalized where he can be protected from suicide. If he does not show a clear-cut response to drug treatment in 1 to 3 weeks, electroconvulsive treatment should be considered immediately.

The combining of two or more stimulants and a tranquilizer in patients who do not respond to these compounds individually certainly requires much more careful study before such an approach can be recommended rationally. The giving of a succession of similar compounds to a patient who does not improve over a period of weeks appears ill-advised. If such a patient does eventually feel better, it is more likely the result of some factor other than the compound which he happened to be receiving at that time.

Fortunately, more effective and safer compounds will continue to be produced. The practitioner will require some impartial source of information about these new products. The recommended source for such information is the yearly volume of *New and Non-Official Drugs,* published by the Council on Drugs of the American Medical Association.

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